DRAFT QUICK SUMMARY

for the

BLOOD PRODUCTS ADVISORY COMMITTEE

82nd Meeting – March 17-18, 2005

The Committee listened to briefings on the recent activities of the DHHS Advisory Committee on Blood Safety and Availability by Dr. Jerry Holmberg, and the Transmissible Spongiform Encephalopathies Advisory Committee by Dr. David Asher. The Committee listened to an update on the West Nile Virus Guidance by Dr. Alan Williams and a summary of the Critical Path Initiative Workshop by Drs. Kathryn Carbone, Paul Mied, and Mary Foulkes, FDA

Topic 1. Safety of Albumin Revisited

Dr. Laurence Landow introduced this topic and provided the Committee with the regulatory background for bringing this issue to the Committee. The FDA had issued a "Dear Doctor" letter in 1998 based on the Cochrane Injuries Group meta-analysis indicating increased mortality with the use of albumin. The Committee then listened to a review of the Cochrane report by Dr. Paul Hebert, Ottawa Health Research Institute, and a review of the SAFE Study by Dr. Simon Finfer, University of Sydney.

The Committee discussed studies on the safety of albumin and some members expressed concerns about the study design behind the original Cochrane report and its limited data. Some members stated that the analysis and conclusions of the study were flawed. Committee members stated that the SAFE study demonstrated that there was essentially no difference between administration of albumin and saline. The Committee requested that more studies should be conducted, so that physicians can make sound health care decisions on the administration of resuscitation fluids. Members stated that there was a need for further well-designed studies investigating the risks of administering albumin to sub groups of patients such as those with trauma and concomitant brain injury**.**

During the first open public hearing portion of the meeting the Dr. Joseph Cervia, Pall Medical, presented information on removal of infectious prions through filtration. Dr. Joseph Latino, LipidViro Tech presented information on inactivation of prions in biological fluids. Mr. Jan Bult, Plasma Protein Therapeutics Association (PPTA) presented industry's position that albumin is safe and the FDA warnings given in the 1998 "Dear Doctor" letter are no longer needed. Dr. Gary Haynes, University of South Carolina reviewed evidence that albumin and saline are therapeutically equivalent as resuscitative therapy for some subsets of patients.

The Committee voted on the following questions:

Have the data from the SAFE study resolved the safety concerns that were raised in the meta-analysis by the Cochrane Group for:

a. Critically ill patients in general?

b. Subgroups of critically ill patients with burns, hypovloemia or hypoalbuminemia?

On part "a" of this question (Critically ill patients in general), the Committee voted: 12 yes votes, 0 no votes, and 0 abstained. The industry representative (IR) agreed with yes votes.

The Committee then reworded part "b" of this question and broke it down into three separate components.

Do currently available data, including those from the SAFE study, resolve safety concerns raised in the 1998 Cochrane Group meta-analysis for subgroups of:

a. **Burns** - The Committee voted: 0 yes votes, 11 no votes, 1 abstained with the IR agreeing with the no votes. Several members commented that their votes should not be taken to imply that they believed the Cochrane Group meta-analysis had established a safety concern for use of albumin in burn patients, given the flaws in the study.
b. **Hypovolemia** - The Committee voted: 12 yes votes, 0 no votes, 0, abstained with the IR agreeing with the yes votes
c. **Hypoalbuminemia** - The Committee voted: 6 yes votes, 3 no votes, 3 abstained and the IR agreeing with the yes votes.

The Committee then listened to an update on international agreements and harmonization by Dr. Mark Weinstein, FDA, and an update on sharing information with the public by Kathleen Swisher, FDA.

Topic 2. Review of Standards for Plasma Products for Transfusion

Dr. Weinstein introduced this topic and a presented a review of the literature. Next, Dr. Irma Szymanski, University of Massachusetts, gave a presentation on the clinical use of plasma.

During the second open public hearing portion of the meeting Dr. Michael Fitzpatrick, America's Blood Centers presented data from surveys of their members on how plasma is currently stored and frozen and the impact on industry if FDA were to change the existing procedures. Kay Gregory, AABB presented their position that there is no current problem with the efficacy of plasma for transfusion and that in the absence of new data there should not be

compelling reasons to require changes in preparation and storage of plasma components. Mr. Joshua Penrod, PPTA stated his association's position that in the absence of science based evidence or a public health concern that FDA should not implement new standards for plasma products.

During the Committee discussion, some Committee members expressed a desire to know how efficacious each of the plasma products are for each of their possible uses. They stated that practicing physicians should be educated in the appropriate use of these products. They also stated that there should be a scientific basis for the use of these products, rather than just continuing established practice. Suggestions were made to form a task group to recommend future research studies so the decisions on use of plasma products would be science based. The question was posed if it was necessary to know the desired clinical effect (or side effects) of these products before FDA attempts to standardize them. Efforts to standardize these products will be difficult since the starting material for plasma products is highly variable and the product itself is different in different places. Some members supported efforts to obtain more product consistency. Several members noted the complexity of plasma as an obstacle to fine characterization relevant to multiple use indications. Members from industry stated that GMP could be used to standardize the product. Other members suggested that plasma products used for transfusion should have to meet certain minimal requirements. The Committee struggled with providing recommendations on products without a basis in science to use for making such decisions. Several BPAC members and members of the public stated that liquid plasma is no longer being used and should be deleted from the regulations.

Topic 3. Study Design for Abbreviated Uniform Donor History Questionnaire

Dr. Sharyn Orton, FDA, introduced the topic and presented the regulatory background for this topic. Then Debra Kessler, from the New York Blood Center presented a proposed study design for the abbreviated uniform donor history questionnaire for frequent donors. Her presentation was followed by a presentation from Mary Beth Bassett, Blood Systems Inc., on their experience with an abbreviated donor history questionnaire.

The committee discussed the design, and intent of the proposed study. Dr. George Schreiber discussed the statistical difference between studies designed to demonstrate equivalence and those to demonstrate discordance. Committee members stated that there will always be risks that will not be caught by any questionnaire. They discussed the diversity of donor questionnaires currently used at different centers and encouraged development of a better questionnaire.

During the third open public hearing portion of the meeting PPTA supported the implementation of an abbreviated donor history questionnaire for frequent donors

and encouraged FDA to respond favorably to AABB's proposal for studying the abbreviated questionnaire.

The Committee modified the first question to read, " **Does the committee agree that the proposed study design (exclusive of sample size) is adequate to demonstrate comparability (or lack of comparability) between the abbreviated questionnaire and the full-length questionnaire?**
The Committee voted on the modified question: 3 yes votes, 9 no votes, and 0 abstained. In explaining their votes the committee members voting either yes or no, did not think that the study was adequately powered.

Since the Committee voted "no" on question one, they did not discuss Question 2 regarding sample size.

Question 3: **If not, what alternative study design and /or sample size does the committee propose would be adequate?** Several Committee members suggested that FDA consider allowing the questionnaire to be implemented with a post approval study with a "stop rule" to reanalyze the study design if needed. Members also requested that consideration be made to evaluating donor retention in this analysis. The committee requested that a cognitive analysis of the two new capture questions on the abbreviated donor questionnaire be performed and that a well designed post implementation study be preformed.

Topic 4. Review of Site Visit Report for the Laboratory of Molecular Virology, DETTD

The Director, Division of Emerging and Transfusion Transmitted Diseases, Dr. Hira Nakhasi, introduced the research being performed in the Laboratory. Then each of the investigators gave a short presentation on their research. The following research summaries were presented:

- Diagnosis and Pathogenesis of HIV variant: a progress report by Dr. Indira Hewlett, Chief, Laboratory of Molecular Virology
- The Molecular Biology of HIV Infection of Primary Human Macrophages by Dr. Andrew Dayton
- Viral and Host Factors in the Pathogenesis of HIV-1 Infection: an overview by Dr. Subhash Dhawan
- West Nile Virus: pathogenesis and diagnostic tools by Dr. Maria Rios, Senior Staff Fellow

In closed session the Committee discussed the site visit report on the above research programs**.**

This summary is provided as an unofficial overview of committee discussions. Please refer to the meeting transcripts for a detailed account of the meeting.